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Multivitamin Freeze-Dried Preparation
[Sōgō Bitamin Tōketsu Kansōzai]

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TITLE (54): MULTIVITAMIN FREEZE-DRIED PREPARATION

FOREIGN TITLE [54A]: SŌGŌ BITAMIN TŌKETSU KANSŌZAI

Specification /1*

1. Title of the Invention

Multivitamin Freeze-Dried Preparation

2. Claim(s)

(1) A multivitamin freeze-dried preparation containing a polyoxyethylene cured castor oil derivative, an excipient and polyhydric alcohol.

3. Detailed Explanation of the Invention

(Industrial Field)

The present invention relates to a multivitamin used by adding it to a high-calorie transfusion used by patients who cannot take nutrition orally following surgery.

(Prior Art)

In recent years, nutrition management of patients who are unable to take nutrition orally following surgery and the like has made great leaps and bounds attendant upon the development of high calorie transfusion therapies using nutrition via the middle cardiac vein and it has become the common practice for administration of a variety of necessary vitamins in high calorie transfusions. Facility of use is extremely important in reducing the workload required for bacterial contamination, prevention of errors in using and preparing by adding it to high calorie transfusion as the performance required for this type of multivitamin preparation. The number of containers used for

* Numbers in the margin indicate pagination in the foreign text.

the preparation must be reduced as much as possible to improve the facility of use and tests have been carried out to stabilize unstable vitamins while providing facility of use. Unexamined Patent 59-152327; and Unexamined Patent 61-207327 disclose a method of freeze-drying (a) a solution to which a group of combined vitamins which are unstable when compounded and (b) an excipient have been added to stabilize it.

Meanwhile, tests have been carried out on freeze-dried preparations or low-temperature vacuum-dried preparations by adding an organic solvent to improve the degree of solubility and to facilitate crystallization in the solvent (Bulletin of Parenteral Drug Association, Vol. 24, page 209 (1970); Unexamined Patent 53-69821, Unexamined Patent 54-73115; and Unexamined Patent 56-120615). However, the prerequisite for organic solvents used in these examples is a solvent which has been removed during depressurization and drying of monovalent lower alcohols and acetones and the like of ethanol and the like. A solvent with a low boiling point is selected and polyhydric alcohol has a high boiling point, crystallization of water is prevented at low temperatures and does not readily become ice. The sample obtained when it is freeze-dried assumes a jelly-like state with extremely inferior outside appearance due to bubbles so /2 that it is not usually used as an additive for a freeze-dried preparation.

(Problems Which the Present Invention is Intended to Solve)

When a fat-soluble vitamin is compounded in a multivitamin to be injected, it must be solubilized using a surface active agent. A polyoxyethylene cured castor oil derivative having low toxicity is optimal for this surface active agent given the toxicity. However, a solution of a multivitamin containing a fat-soluble vitamin which can be solubilized using this polyoxyethylene cured castor oil or derivative was characteristic in that when an excipient was added to stabilize it and freeze-dry it, there were problems in that turbidity occurred when it was again dissolved or the time up to when a dissolution solution was added and a clear solution was obtained was lengthened. A method has been devised (Unexamined Patent 62-38) to solve these problems which involves not adding an excipient and compounding a polyoxypropylene multivitamin non-ionic surface active agent and a phospholipid as a dissolution assisting agent with the polyoxyethylene cured castor oil derivative and not adding an excipient.

In this method, not adding an excipient to promote stabilization of the vitamin is a necessary condition. The stability of the vitamins must be sacrificed to upgrade the resolubility. As a result, an excipient must be compounded to maintain the stability of the solubilized freeze-dried preparation using a polyoxyethylene cured castor oil derivative.

(Means Used to Solve the Problems)

After carrying out a variety of studies, the inventors found that a multivitamin freeze-dried preparation with good stability, resolubilizing characteristics and good outside appearance can be obtained by compounding a polyoxyethylene cured castor oil derivative in the multivitamin freeze-dried preparation.

The present invention was completed based on the abovementioned findings. There are no particular restrictions on the vitamins to be used in the multivitamin and any conventionally well-known vitamin may be used. For example, vitamins B_1, B_2, B_6, B_{12}, folic acid, nicotinic acid or amide nicotinate, pantothenic acid or pantothenyl alcohol, biotin as well as vitamin C may be used. Moreover, a fat-soluble vitamin to which a suitable solubilizing agent has been added may be added to these vitamins. Vitamins A, D, E and or vitamin K may be used as the fat-soluble vitamin. There are no particular restrictions on the amount of these vitamins to be added, however, an amount which is close to the daily requirement for humans should be compounded. Examples of the amounts of the respective vitamins to be added should be compounded in the following proportions: vitamin B_2, 1 to 10 mg; vitamin B_6, 1 to 10 mg; pantothenic acid, 5 to 25 mg; vitamin C, 50 to 250 mg; vitamin B_1, 1 to 10 mg; vitamin B_{12}, 1 to 30 μg; folic acid, 100 to 1000 μg; biotin, 20 to 300 μg; nicotinic acid, 10 to 50 mg; vitamin A, 2000 to 5000 IU; vitamin D, 200 to 1000 IU; vitamin E, 5 to 20 IU; and vitamin K, 0.2 to 10 mg.

Specific examples of the amount compounded are indicated in Table 1.

Table 1 Examples of Amounts of Vitamin Constituents Compounded in Multivitamin

Vitamin	Amount Compounded
vitamin B_1 (thiamine hydrochloride)	3 mg
vitamin B_2 (riboflavin sodium phosphate)	5 mg
vitamin B_6 (pyridoxine hydrochloride)	4 mg
vitamin B_{12} (cyanocobalamine)	10 μg
amide nicotinate	40 mg
Panthenol	14 mg
folic acid	400 μg
Biotin	100 μg
vitamin C (ascorbic acid)	100 mg
vitamin A (retinol palmitate)	3300 IU
vitamin D_2 (ergocalciphenol)	400 IU
vitamin E (tocopheral acetate)	15 mg
vitamin K_1 (phytonadione)	2 mg

HCO 10, 50, 60, 100 and the like may be used as the polyoxyethylene cured castor oil derivative regardless of the molecular weight. The amount used should be 5 to 50 % and preferably approximately 8 to 30 % relative to the entire amount of the /3 preparation. Mannitol and other sugar alcohols, lactose, maltose and other monosaccharides, oligosaccharides, histidine, arginine and other amino acids, condroitin sulfate, dextran and other polymers may be used. The amount to be used should be 5 to 75 % and preferably 20 to 70% relative to the entire amount of the preparation.

Glycerol, propylene glycol, liquid- or ointment-form polyethylene glycol and the like having a molecular weight of 200 to

1500 may be used at ordinary temperature. The amount used should be approximately 1 to 15 w/w % and preferably approximately 5 to 15 w/w % relative to the overall amount of the preparation.

The present invention can be prepared using the regular method used to prepare an injection-use agent. Therefore, a water-soluble vitamin and excipient are dissolved in injection-use distilled water and the pH is regulated to 4.5 to 6.5 using sodium hydroxide and other pH regulators. Separately, the fat-soluble vitamins are solubilized in water to which a polyoxyethylene cured castor oil derivative has been added. Next, we added polyhydric alcohol and adjusted an aqueous solution of the fat-soluble vitamins. We mixed both of these so that they were uniform. We made small portions of these and freeze-dried them and obtained the freeze-dried preparation in the present invention.

It was found that the greater the weight ratio of the alcohol, the greater the improvement and the clarity of the resolubilized solution increased.

We used examples in which no solubilizing assistant was contained and examples in which approximately 20 % of a solubilizing agent was contained as practical examples and a control example of the present invention.

(Effect of Invention)

The outside appearance of the samples in the practical examples of the present invention and the control sample as well as the

outside appearance of the solution which had been resolubilized are indicated in Table 2.

The outside appearance of the samples in all of the practical examples of the present invention was good and the outside appearance of the resolubilized solution was satisfactory as well. However, despite the fact that the outside appearance of the sample in the control example which did not contain the solubilizing assistant was good, the resolubilized solution was turbid.

Table 2 Outside Appearance of Multivitamin Freeze-dried Preparation and Resolubilizing Characteristics

Number	Solubilizing Assistant Type/amount added (mg)	Outside Appearance of Freeze-dried Cake	Outside Appearance of Second Dissolved Solution
PE 1	10 mg of propylene glycol	yellowish brown spongy clumps	faint yellow clear liquid
PE 2	30 mg of propylene glycol	Same as above	faint yellow clear liquid
PE 3	15 mg of glycerol	Same as above	faint yellow clear liquid
PE 4	20 mg of polyethylene glycol 400	Same as above	faint yellow clear liquid
CE 1	solubilizing assistant not added	Same as above	faint yellow; somewhat brown liquid

PE: Practical Example; CE: Control Example

(Note) outside appearance of solution to which 5 ml of injection-use distilled water per vial had been added.

Practical Example 1

We dissolved the water-soluble vitamins in injection-use distilled water according to the amount of the vitamins indicated in Table 1 which had been compounded. We added 50 mg of lactose as an

excipient to this solution and dissolved it. Moreover, we solubilized the fat-soluble vitamins in injection-use distilled water using 80 mg of polyoxyethylene cured castor oil 60 and further added 10 mg of propylene glycol. We mixed both of these solutions, adjusted the pH to 5.5 using sodium hydroxide and made the entire amount 3 ml. We packed the chemical solution obtained in a vial, freeze-dried it, then closed it with a rubber stopper and obtained the product in the present invention.

Practical Example 2

We carried out the same operations as in Practical Example 1 using 30 mg of propylene glycol instead of the 10 mg in Practical Example 1 and obtained the product in the present invention.

Practical Example 3

We carried out the same operations as in Practical Example 1 except that we used 15 mg of concentrated glycerol instead of the 10 mg of propylene glycol in Practical Example 1 and we obtained the product in the present invention.

Practical Example 4

We carried out the same operations as in Practical Example 1 except that we used 20 mg of polyethylene glycol 400 instead of the 10 mg of the propylene glycol in Practical Example 1 and obtained the product in the present invention.

Comparative Control Example 1

We carried out the same operations as Practical Example 1 except that we added propylene glycol and we obtained a comparative control product.